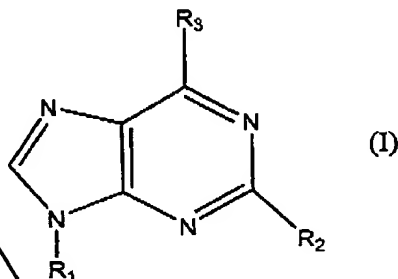


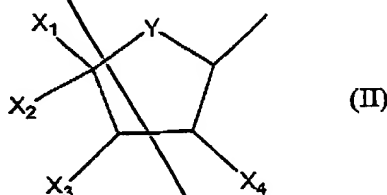
CLAIMS:

- Subt
A22
1. A method for activating natural killer (NK) cells in an individual comprising administering said individual with an effective amount of one or more adenosine A3 receptor agonists (A3RAg).
 2. The method of Claim 1, wherein said A3RAg is a compound of the general formula (I):



wherein,

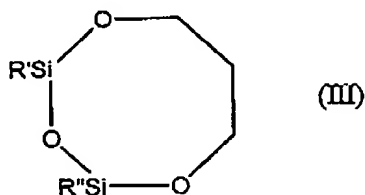
- R_1 represents an alkyl, hydroxyalkyl, carboxyalkyl or cyanoalkyl or a group of the following general formula (II):



in which:

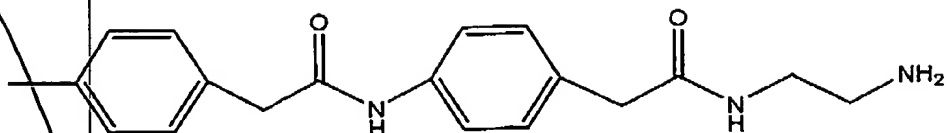
- Y represents an oxygen, sulfur or carbon atom;
- X_1 represents H, alkyl, $R^a R^b NC(=O)-$ or HOR^c- , wherein
- R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl or are joined together to form a heterocyclic ring containing two to five carbon atoms; and

- R^c is selected from the group consisting of alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl;
- X_2 is H, hydroxyl, alkylamino, alkylamido or hydroxyalkyl;
- X_3 and X_4 represent independently hydrogen, hydroxyl, amino, amido, azido, halo, alkyl, alkoxy, carboxy, nitrilo, nitro, trifluoro, aryl, alkaryl, thio, thioester, thioether, -OCOPh, -OC(=S)OPh or both X_3 and X_4 are oxygens connected to $>C=S$ to form a 5-membered ring, or X_2 and X_3 form the ring of formula (III):



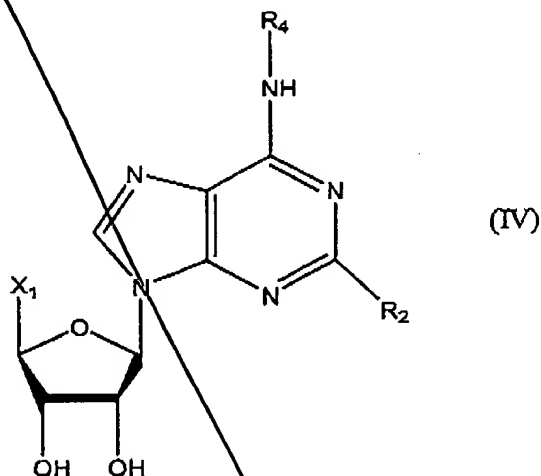
where R' and R'' represent independently an alkyl group;

- R_2 is selected from the group consisting of hydrogen, halo, alkylether, amino, hydrazido, alkylamino, alkoxy, thioalkoxy, pyridylthio, alkenyl; alkynyl, thio, and alkylthio; and
- R_3 is a group of the formula $-NR_4R_5$ wherein
- R_4 is a hydrogen atom or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with Z being O, S, or NR^a with R^a having the above meanings; wherein when R_4 is hydrogen then
- R_5 is selected from the group consisting of R- and S-1-phenylethyl, benzyl, phenylethyl or anilide groups unsubstituted or substituted in one or more positions with a substituent selected from the group consisting of alkyl, amino, halo, haloalkyl, nitro, hydroxyl, acetoamido, alkoxy, and sulfonic acid or a salt thereof; benzodioxanemethyl, fururyl, L-propylalanylaminobenzyl, β -alanylaminobenzyl, T-BOC- β -alanylaminobenzyl, phenylamino, carbamoyl, phenoxy or cycloalkyl; or R_5 is a group of the following formula:



or when R_4 is an alkyl or aryl-NH-C(Z)-, then, R_5 is selected from the group consisting of heteroaryl-NR^a-C(Z)-, heteroaryl-C(Z)-, alkaryl-NR^a-C(Z)-, alkaryl-C(Z)-, aryl-NR-C(Z)- and aryl-C(Z)-; Z representing an oxygen, sulfur or amine;
or a pharmaceutically acceptable salt of the above compound.

3. The method of Claim 2, wherein said A3Rag is a nucleoside derivative of the general formula (IV):



10 wherein X_1 , R_2 and R_4 are as defined in Claim 2.

4. The method of Claim 3, wherein A3Rag is selected from the group consisting of N⁶-2-(4-aminophenyl)ethyladenosine (APNEA), N⁶-(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and N⁶-(2-iodobenzyl)-adenosine-5'-N-methyluronamide (IB-MECA) and 2-chloro-N⁶-(2-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA).

5. The method of Claim 4, wherein A3Rag is IB-MECA or Cl-IB-MECA.

6. The method of Claim 1, wherein said A3Rag is N⁶-benzyladenosine-5'-N-alkyluronamide-N¹-oxide or N⁶-benzyladenosine-5'-N-dialkyluronamide-N¹-oxide,

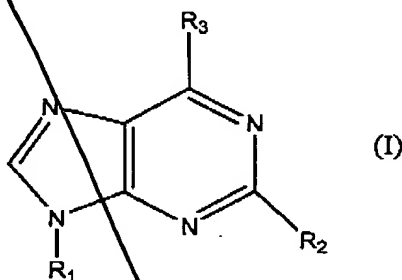
both optionally substituted at the 2-purine position with an alkoxy, amino, alkenyl, alkynyl or halogenoxide group.

7. The method of Claim 1 wherein said A3RAg is administered orally to said individual.

5 8. The method of Claim 1, wherein said A3RAg is injected to said individual.

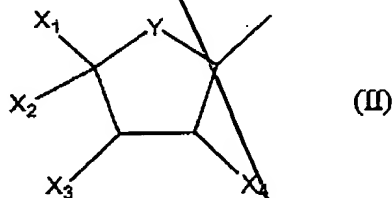
9. A method for a therapeutic treatment comprising administering to an individual in need, one or more A3RAg in an amount effective for achieving a therapeutic effect, the therapeutic effect comprises activation of NK cells in said individual.

10 10. The method of Claim 9, wherein said A3RAg is a compound of the general formula (I):



wherein,

- R₁ represents an alkyl, hydroxyalkyl, carboxyalkyl or cyanoalkyl or a
15 group of the following general formula (II):



in which:

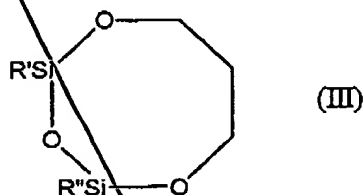
- Y represents an oxygen, sulfur or carbon atom;
- X₁ represents H, alkyl, R^aR^bNC(=O)- or HOR^c-, wherein

- R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl or are joined together to form a heterocyclic ring containing two to five carbon atoms; and

5 - R^c is selected from the group consisting of alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl;

- X_2 is H, hydroxyl, alkylamino, alkylamido or hydroxyalkyl;

10 - X_3 and X_4 represent independently hydrogen, hydroxyl, amino, amido, azido, halo, alkyl, alkoxy, carboxy, nitrilo, nitro, trifluoro, aryl, alkaryl, thio, thioester, thioether, -OCOPh, -OC(=S)OPh or both X_3 and X_4 are oxygens connected to $>C=S$ to form a 5-membered ring, or X_2 and X_3 form the ring of formula (III):



where R' and R'' represent independently an alkyl group;

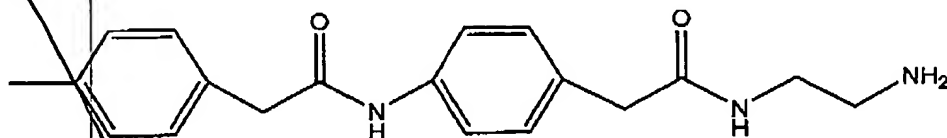
15 - R_2 is selected from the group consisting of hydrogen, halo, alkylether, amino, hydrazido, alkylamino, alkoxy, thioalkoxy, pyridylthio, alkenyl; alkynyl, thio, and alkylthio; and

- R_3 is a group of the formula $-NR_4R_5$ wherein

20 - R_4 is a hydrogen atom or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with Z being O, S, or NR^a with R^a having the above meanings; wherein when R_4 is hydrogen then

25 - R_5 is selected from the group consisting of R- and S-1-phenylethyl, benzyl, phenylethyl or anilide groups unsubstituted or substituted in one or more positions with a substituent selected from the group consisting of alkyl, amino, halo, haloalkyl, nitro, hydroxyl, acetoamido, alkoxy, and sulfonic acid or a salt thereof;

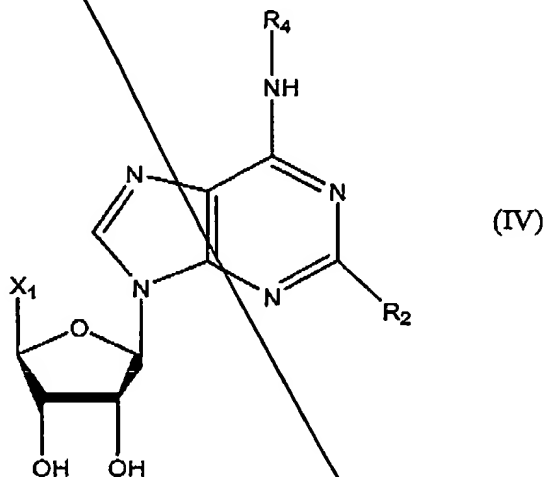
benzodioxanemethyl, fururyl, L-propylalanyl- aminobenzyl, β -alanyl-amino- benzyl, T-BOC- β -alanylaminobenzyl, phenylamino, carbamoyl, phenoxy or cycloalkyl; or R_5 is a group of the following formula:



- 5 or when R_4 is an alkyl or aryl-NH-C(Z)-, then, R_5 is selected from the group consisting of heteroaryl-NR^a-C(Z)-, heteroaryl-C(Z)-, alkaryl-NR^a-C(Z)-, alkaryl-C(Z)-, aryl-NR-C(Z)- and aryl-C(Z)-; Z representing an oxygen, sulfur or amine;

or a pharmaceutically acceptable salt of the above compound.

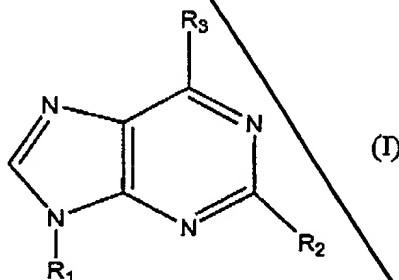
- 10 11. The method of Claim 10, wherein said A3Rag is a nucleoside derivative of the general formula (IV):



wherein X_1 , R_2 and R_4 are as defined.

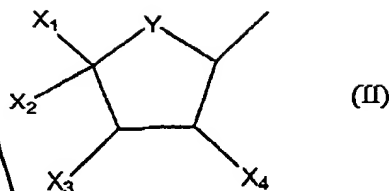
12. The method of Claim 11, wherein said A3Rag is selected from the group consisting of N⁶-2-(4-aminophenyl)ethyladenosine (APNEA), N⁶-(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and N⁶-(2-iodobenzyl)-adenosine- 5'-N-methyluronamide (IB-MECA) and 2-chloro-N⁶-(2-iodobenzyl)-adenosine- 5'-N-methyluronamide (Cl-IB-MECA).

13. The method of Claim 12, wherein said A3RAg is Cl-IB-MECA.
14. The method of Claim 9, wherein said A3RAg is N⁶-benzyladenosine-5'-N-alkyluronamide-N¹-oxide or N⁶-benzyladenosine-5'-N-dialkyluronamide-N¹-oxide, both optionally substituted at the 2-purine position with an alkoxy, amino, alkenyl, alkynyl or halogenoxide group.
15. The method of Claim 9, wherein said A3RAg is orally administered to said individual.
16. The method of Claim 9, wherein said A3RAg is injected to said individual.
17. A method for treatment of a disease comprising administering to an individual in need of such treatment NK cells *a priori* activated with an effective amount of at least one A3RAg.
18. The method according to Claim 17, wherein said NK cells are autologous cells, the method comprising withdrawing NK cells from the individual, contacting said cells with an amount of an A3RAg effective to activate said NK cells and injecting the activated NK cells to the individual.
19. The method of Claim 17, wherein said A3RAg is a compound of the general formula (I):



wherein,

- 20 - R₁ represents an alkyl, hydroxyalkyl, carboxyalkyl or cyanoalkyl or a group of the following general formula (II):



in which:

- Y represents an oxygen, sulfur or carbon atom;
- X_1 represents H, alkyl, $R^a R^b NC(=O)-$ or HOR^c- , wherein
 - R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl or are joined together to form a heterocyclic ring containing two to five carbon atoms; and
 - R^c is selected from the group consisting of alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl;
- X_2 is H, hydroxyl, alkylamino, alkylamido or hydroxyalkyl;
- X_3 and X_4 represent independently hydrogen, hydroxyl, amino, amido, azido, halo, alkyl, alkoxy, carboxy, nitrilo, nitro, trifluoro, aryl, alkaryl, thio, thioester, thioether, $-OCOPh$, $-OC(=S)OPh$ or both X_3 and X_4 are oxygens connected to $>C=S$ to form a 5-membered ring, or X_2 and X_3 form the ring of formula (III):

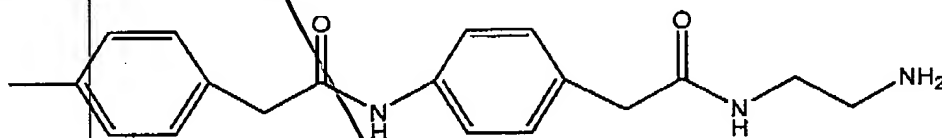


where R' and R'' represent independently an alkyl group;

- R_2 is selected from the group consisting of hydrogen, halo, alkylether, amino, hydrazido, alkylamino, alkoxy, thioalkoxy, pyridylthio, alkenyl, alkynyl, thio, and alkylthio; and
- R_3 is a group of the formula $-NR_4R_5$ wherein

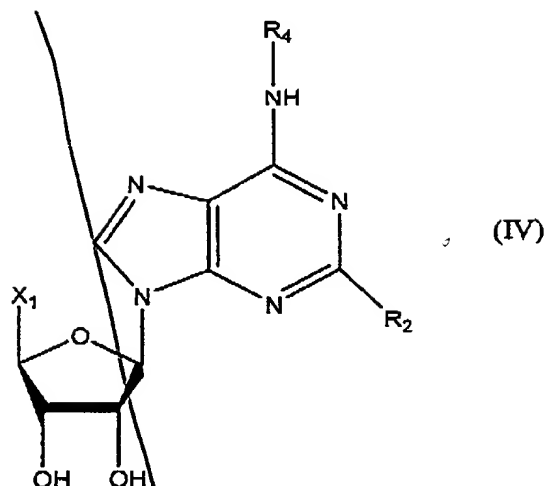
- R_4 is a hydrogen atom or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with Z being O, S, or NR^a with R^a having the above meanings; wherein when R_4 is hydrogen then

- R_5 is selected from the group consisting of R- and S-1-phenylethyl, benzyl, phenylethyl or anilide groups unsubstituted or substituted in one or more positions with a substituent selected from the group consisting of alkyl, amino, halo, haloalkyl, nitro, hydroxyl, acetoamido, alkoxy, and sulfonic acid or a salt thereof; benzodioxanemethyl, furanyl, L-propylalanyl- aminobenzyl, β -alanyl-amino- benzyl, T-BOC- β -alanylaminobenzyl, phenylamino, carbamoyl, phenoxy or cycloalkyl; or
10 R_5 is a group of the following formula:



or when R_4 is an alkyl or aryl-NH-C(Z)-, then, R_5 is selected from the group consisting of heteroaryl- NR^a -C(Z)-, heteroaryl-C(Z)-, alkaryl- NR^a -C(Z)-, alkaryl-C(Z)-, aryl- NR -C(Z)- and aryl-C(Z)-; Z representing an oxygen, sulfur or
15 amine;
or a pharmaceutically acceptable salt of the above compound.

20. The method of Claim 19, wherein said A3RAG is a nucleoside derivative of the general formula (IV):

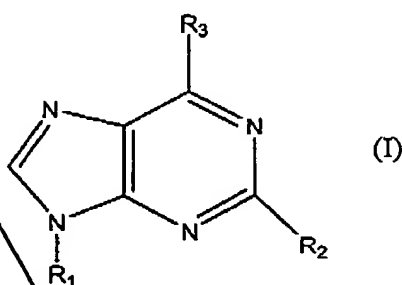


wherein X_1 , R_2 and R_4 are as defined.

21. The method of Claim 20, wherein said A3Rag is selected from the group consisting of N^6 -2-(4-aminophenyl)ethyladenosine (APNEA),
5 N^6 -(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and N^6 -(2-iodobenzyl)-adenosine-5'-N-methyluronamide (IB-MECA) and 2-chloro- N^6 -(2-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA).
22. The method of Claim 21, wherein said A3Rag is Cl-IB-MECA.
23. The method of Claim 17, wherein said A3Rag is N^6 -benzyladenosine-5'-
10 N-alkyluronamide- N^1 -oxide or N^6 -benzyladenosine-5'-N-dialkyluronamide- N^1 -oxide, both optionally substituted at the 2-purine position with an alkoxy, amino, alkenyl, alkynyl or halogenoxide group.
24. The method of Claim 17, comprising administering an amount of an A3Rag to a donor individual effective to activate the NK cells in the donor individual,
15 withdrawing the activated NK cells from the donor individual and administering the activated NK cells to a recipient individual.
25. The method of Claim 24, wherein said A3Rag is orally administered to said donor individual.
26. The method of Claim 24, wherein said A3Rag is administered to said donor
20 individual by injection.

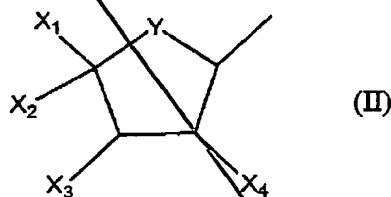
✓ 27. A pharmaceutical composition comprising one or more A3Rag in an amount effective to achieve a therapeutic effect, the therapeutic effect comprising activation of NK cells, the pharmaceutical composition optionally comprising physiologically acceptable additives.

5 28. The pharmaceutical composition of Claim 27, wherein said A3Rag is a compound of the general formula (I):



wherein,

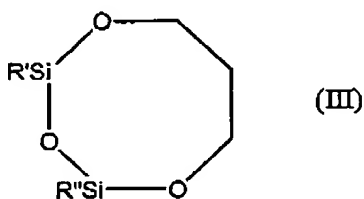
- R₁ represents an alkyl, hydroxyalkyl, carboxyalkyl or cyanoalkyl or a
10 group of the following general formula (II):



in which:

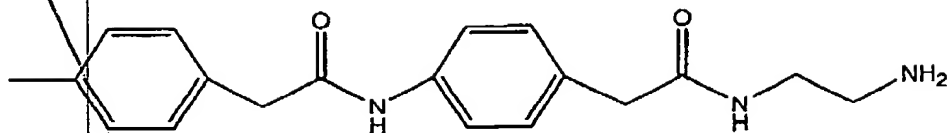
- Y represents an oxygen, sulfur or carbon atom;
- X₁ represents H, alkyl, R^aR^bNC(=O)- or HOR^c-, wherein
- 15 - R^a and R^b may be the same or different and are selected from the group consisting of hydrogen, alkyl, amino, haloalkyl, aminoalkyl, BOC-aminoalkyl, and cycloalkyl or are joined together to form a heterocyclic ring containing two to five carbon atoms; and
- R^c is selected from the group consisting of alkyl, amino, haloalkyl,
- 20 aminoalkyl, BOC-aminoalkyl, and cycloalkyl;

- X_2 is H, hydroxyl, alkylamino, alkylamido or hydroxyalkyl;
- X_3 and X_4 represent independently hydrogen, hydroxyl, amino, amido, azido, halo, alkyl, alkoxy, carboxy, nitrilo, nitro, trifluoro, aryl, alkaryl, thio, thioester, thioether, -OCOPh, -OC(=S)OPh or both X_3 and X_4 are oxygens connected to $>C=S$ to form a 5-membered ring, or X_2 and X_3 form the ring of formula (III):



where R' and R'' represent independently an alkyl group;

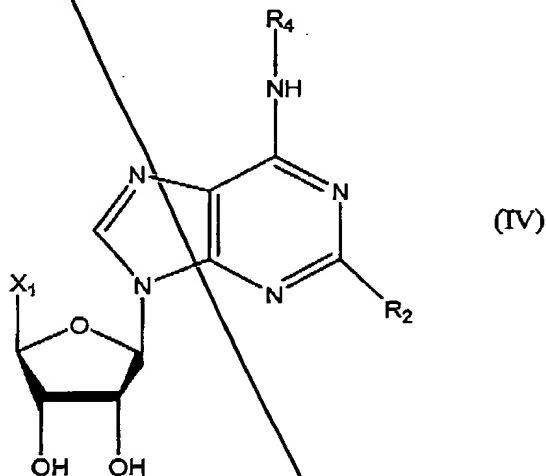
- R_2 is selected from the group consisting of hydrogen, halo, alkylether, amino, hydrazido, alkylamino, alkoxy, thioalkoxy, pyridylthio, alkenyl, alkynyl, thio, and alkylthio; and
- R_3 is a group of the formula $-NR_4R_5$ wherein
 - R_4 is a hydrogen atom or a group selected from alkyl, substituted alkyl or aryl-NH-C(Z)-, with Z being O, S, or NR^a with R^a having the above meanings; wherein when R_4 is hydrogen then
 - R_5 is selected from the group consisting of R- and S-1-phenylethyl, benzyl, phenylethyl or anilide groups unsubstituted or substituted in one or more positions with a substituent selected from the group consisting of alkyl, amino, halo, haloalkyl, nitro, hydroxyl, acetoamido, alkoxy, and sulfonic acid or a salt thereof; benzodioxanemethyl, fururyl, L-propylalanyl-aminobenzyl, β -alanyl-amino- benzyl, T-BOC- β -alanylaminobenzyl, phenylamino, carbamoyl, phenoxy or cycloalkyl; or R_5 is a group of the following formula:



or when R_4 is an alkyl or aryl-NH-C(Z)-, then, R_5 is selected from the group consisting of heteroaryl-NR^a-C(Z)-, heteroaryl-C(Z)-, alkaryl-NR^a-C(Z)-, alkaryl-C(Z)-, aryl-NR-C(Z)- and aryl-C(Z)-; Z representing an oxygen, sulfur or amine;

or a pharmaceutically acceptable salt of the above compound.

29. The pharmaceutical composition of Claim 28, wherein said A3Rag is a nucleoside derivative of the general formula (IV):



10 wherein X_1 , R_2 and R_4 are as defined in Claim 2.

30. The pharmaceutical composition of Claim 29, wherein A3Rag is selected from the group consisting of N⁶-2-(4-aminophenyl)ethyladenosine (APNEA), N⁶-(4-amino-3-iodobenzyl) adenosine-5'-(N-methyluronamide) (AB-MECA) and N⁶-(2-iodobenzyl)-adenosine-5'-N-methyluronamide (IB-MECA) and 2-chloro-N⁶-(2-iodobenzyl)-adenosine-5'-N-methyluronamide (Cl-IB-MECA).

31. The pharmaceutical composition of Claim 30, wherein A3Rag is Cl-IB-MECA.

32. The pharmaceutical composition of Claim 27, wherein said A3RAg is N⁶-benzyladenosine-5'-N-alkyluronamide-N¹-oxide or N⁶-benzyladenosine-5'-N-dialkyluronamide-N¹-oxide, both optionally substituted at the 2-purine position with an alkoxy, amino, alkenyl, alkynyl or halogenoxide group.
- 5 33. The pharmaceutical composition of Claim 27, wherein said A3RAg is formulated for oral administration to said individual.
34. The pharmaceutical composition of Claim 27, wherein said A3RAg is formulated for injection to said individual.
35. The pharmaceutical composition of Claim 27, in a single dosage unit form.